

REMARKS

Status of the claims

Claims 1-5, 22-28, 30-48 and 52-57 were pending. By amendment herein, claim 22 has been canceled, without prejudice or disclaimer. Thus, claims 1-5, 23-28, 30-48 and 52-57 are pending as shown above and claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-54 are under consideration.

Rejections Withdrawn

Applicants note with appreciation that the rejections under 35 U.S.C. § 102 have been withdrawn.

Claim Objections

Claim 22 was objected to for being of improper dependent form in failing to further limit claim 30. (Office Action, page 3).

Applicants thank the Examiner for the careful attention to the claims and have cancelled claim 22 by amendment herein, thereby rendering the objection moot.

Double Patenting

Claims 2, 4, 25-28, 30-32, 36, 37, 39-41 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 12-14, 18, 25 and 27 of U.S. Patent No. 7,273,923. (Office Action, pages 3-5).

Submitted herewith is a Terminal Disclaimer over U.S. Patent No. 7,273,923. Thus, the rejection has been obviated.

35 U.S.C. § 112, 2nd paragraph

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57 were newly rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting “non-naturally occurring” (Office Action, pages 5-7):

The term is unclear in that it is used to describe the zinc-finger binding protein encoded by the claimed polynucleotide, and more specifically the recognition helix of a zinc-finger binding domain within the protein. The structures provided in the instant application apply equally to naturally occurring and non-naturally occurring zinc finger proteins, and there is nothing in the claim or specification to define the metes and bounds of the non-naturally occurring recognition helices or zinc finger domains. It is impossible to know whether any given sequence is within the scope of the claims without knowing whether it is found in nature. Given that proteins in nature are constantly changing, there is no way to know whether any given sequence is found in nature.

Applicants traverse the rejection and supporting remarks.

The definiteness of the term “non-naturally occurring” must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art and (3) claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *See, e.g., Energizer Holdings, Inc. v. ITC*, 77 USPQ2d 1625 (Fed. Cir. 2006). In other words, the terms at issue must be read in context of the application and field of endeavor.

In the instant case, the contention that the “structures” provided do not distinguish between naturally and non-naturally occurring is unfounded. The “structure” claimed is a zinc finger protein with the recited zinc coordinating residues and with a non-naturally occurring recognition helix. Zinc finger proteins (i.e. structures) with non-canonical fingers having naturally occurring recognition helix are plainly excluded by the claims.

Moreover, the specification and state of the art clearly establish that the skilled artisan would readily understand the metes and bounds of the term “non-naturally occurring” as applied to a zinc finger protein. The specification clearly defines the term “non-naturally occurring” as follows (page 10, lines 30-31):

The term “naturally-occurring” is used to describe an object that can be found in nature, as distinct from being artificially produced by a human.

In addition, the as-filed specification more than clearly defines what is encompassed by the recitation “the recognition region of zinc-finger binding domain protein is non-naturally occurring and is engineered to bind to a target sequence in a plant cell.” Specifically, this term clearly refers to zinc finger proteins which have been altered in the recognition region helix by design or selection to bind to a selected target site. See, e.g., page 10, lines 17-29; Example 1 on page 45; Example 4, emphasis added:

A "modified" zinc finger protein is a protein not occurring in nature that has been designed and/or selected so as to comprise a substitution of at least one amino acid, compared to a naturally occurring zinc finger protein. Further, a “designed” zinc finger protein is a protein not occurring in nature whose structure and composition results principally from rational criteria. Rational criteria for design include application of substitution rules and computerized algorithms for processing information in a database storing information of existing ZFP designs and binding data, for example as described in co-owned PCT WO 00/42219. A “selected” zinc finger protein is a protein not found in nature whose production results primarily from an empirical process such as phage display. See e.g., US 5,789,538; U.S. 6,007,988; U.S. 6,013,453; WO 95/19431; WO 96/06166 and WO 98/54311. Designed and/or selected ZFPs are also referred to as "engineered" ZFPs and can be modified according to the methods and compositions disclosed herein (e.g., by conversion to C3H and/or to comprise a plant backbone).

Synthetic genes encoding non-canonical zinc finger binding proteins are obtained following the procedure outlined in co-owned PCT WO 00/42219, with the exception that the oligonucleotide encoding the recognition helix to be modified includes a polynucleotide sequence that specifies the modified amino acid sequence. For example, for modification of finger 3 (the C-terminal-most finger of a three-finger ZFP), the sequence of oligonucleotide 6 is designed to encode the modified zinc coordination residue(s).

A search was conducted for plant zinc fingers whose backbone sequences (i.e., the portion of the zinc finger outside of the -1 through +6 portion of the recognition helix) resembled that of the SP-1 consensus sequence described by Berg (1992) Proc. Natl. Acad. Sci. USA 89:11,109-11,110. The sequences selected included the two conserved cysteine residues, a conserved basic residue (lysine or arginine) located two residues to the C-terminal side of the second (i.e. C-terminal) cysteine, a conserved phenylalanine residue located two residues to the C-terminal side of the basic residue, the two conserved histidine residues, and a conserved arginine residue located two residues to the C-terminal side of the first (i.e., N-terminal) conserved histidine. The amino acid sequences of these selected plant zinc finger backbones (compared to the SP-1 consensus sequence) are shown below, with conserved residues shown in bold and X referring to residues located at positions -1 through +6 in the recognition helix (which will differ among different proteins depending upon the target sequence) ... Amino acid residues denoted by X, present in the recognition portion of these zinc fingers, are designed or selected depending upon the desired target site, according to methods disclosed, for example, in co-owned WO 00/41566 and WO 00/42219, and/or references cited *supra*.

Oligonucleotides H1, H2 and H3 (below) comprise sequences corresponding to the reverse complement of the recognition helices of fingers 1-3 respectively; accordingly, nucleotides denoted by N vary depending upon the desired amino acid sequences of the recognition helices, which, in turn, depend upon the nucleotide sequence of the target site.

Furthermore, the state of the art at the time of filing clearly evidences that the skilled artisan would understand that the metes and bounds of a zinc finger protein having a non-naturally occurring recognition helix. See, e.g., 7,273,923; 7,262,054; 7,253,273; 7,163,824; 7,070,934; 7,013,219; 6,979,539; 6,824,978; 6,607,882; 6,599,692; and 6,534,261. For example, Shi et al. (Ref. C123 of IDS submitted May 9, 2005 and considered by the Examiner on November 12, 2005), compares the properties of

“natural” zinc finger proteins and “designed” zinc finger proteins (i.e., zinc finger proteins having alterations in the non-DNA binding residues). Thus, it is clear that the skilled artisan, at the time of filing, was well aware that designed zinc finger DNA-binding domains were non-naturally occurring.

Applicants also again direct the Examiner’s attention to the recent decision by the Board of Patent Appeals and Interferences, where the Board confirmed that that the phrase “naturally occurring” would clearly be understood by the skilled artisan to mean something that exists or is found in nature. See, *Ex parte Dewis* (Appeal 2007-1610, decided September 4, 2007). Indeed, the Examiner acknowledges on page 13 of the Office Action that “one of skill would understand ‘non-naturally occurring’ to mean not found in nature.” Therefore, the skilled artisan would have no doubt as to the scope of the term “non-naturally occurring,” namely to engineered zinc finger proteins that are not found in nature.

Finally, the Examiner’s assertion that it is “impossible” to know whether any sequence is naturally occurring because not all naturally occurring proteins are known and because proteins change over time is incorrect and does not support the contention that the claims are indefinite. Zinc finger proteins can be naturally-occurring or they can be non-naturally-occurring; the claims make explicit that the recognition helices of the zinc finger proteins of the claims are non-naturally-occurring. Furthermore, at any point in time, it is a simple and straightforward matter for one of skill in the art to determine what is or is not naturally-occurring; thereby determining what is encompassed by the claims.

Thus, in view of the specification as a whole and state of the art, the claims are clear and withdrawal of the rejection is in order.

35 U.S.C. § 112, first paragraph, written description

Claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-56 were again rejected under 35 U.S. C. § 112, first paragraph as allegedly failing to comply with the written description requirement. (Office Action, pages 7-14). The Examiner continues to assert that (Office Action, pages 13-14):

[t]he claims do not sufficiently distinguish between naturally occurring and non-naturally occurring proteins in that the structure of any claimed zinc finger recognition helix or region may be found in nature. A complete description of all naturally occurring proteins is not provided for comparison, and sequences found in nature are constantly changing as a result of naturally-occurring spontaneous mutations. Thus, it is impossible to know whether any given sequence is found in nature.

The Examiner's assertion that Applicants are somehow required to describe that which is excluded by the claims (i.e. "a complete description of all naturally occurring proteins ... for comparison") is completely improper. The written description requirement is satisfied when the as-filed specification, in light of the knowledge possessed by the skilled artisan at the time of filing, reasonably conveys that Applicants were in possession of the claimed subject matter, in this case a non-canonical zinc finger domain with a non-naturally occurring, engineered recognition helix. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971); *In re Lange*, 209 USPQ 288 (CCPA 1981). Not only must the disclosure be read in light of the knowledge possessed by one of skill in the art, but the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976).

For the reasons of record and noted above with regard to definiteness, the specification as filed clearly conveys that Applicants were in possession of the claimed subject matter. The specification provides detailed description of zinc finger protein, structure, including engineering of non-naturally occurring recognition helices to target binding of the claimed zinc finger proteins to any desired target site. *See, e.g.,* page 10 and Examples.

Furthermore, the state of the art clearly establishes that Applicants were in possession of zinc finger proteins with non-naturally occurring recognition helices at the time of filing. The art of record clearly establishes that non-naturally occurring recognition helices are those that differ in structure (amino acid sequence) from naturally

occurring structures. See, e.g., U.S. Patent No. 5,789,538 (Reference A26 of IDS mailed on May 9, 2005); U.S. Patent No. 6,013,453 (Issued January 11, 2000; Reference A3 of IDS mailed on April 11, 2003); and WO 00/41566 (published July 20, 2000; Reference B20 of IDS mailed on May 9, 2005). These and other references, which were available at the time of filing, show that one of skill in the art would have understood that Applicants were in possession of zinc finger proteins containing non-naturally-occurring recognition helices, as claimed.

Likewise, the assertion that “the structure of any claimed zinc finger recognition helix or region may be found in nature” is factually erroneous. In the instant claims, the structure is the amino acid sequence. As clearly established by the evidence of record, it can readily be determined if the recognition helices resulting from engineering (design and/or selection) are non-naturally occurring.

Thus, when properly construed, the claims are adequately described, as set forth above and acknowledged by the Office. Accordingly, the rejection should be withdrawn.

35 U.S.C. § 103

Claims 2, 4, 22, 25-28, 30-32, 36-37, 39-41 and 53-55 were newly rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 7,151,201 (hereinafter “Barbas”) in view of Green et al. (1998) *Biochem. J.* 333:85-90 (hereinafter “Green”). (Office Action, pages 15-20). In addition, claim 37 was rejected as allegedly obvious over Barbas in view of Green and in further view of Guyder. (Office Action, pages 20-22). Barbas was cited for teaching C2H2 zinc finger proteins with engineered recognition helices and Green was cited for teaching that C2H2 zinc finger proteins that were altered to C4 proteins bind to their cognate target sites. *Id.*

The pending claims require that the zinc coordinating residues of the zinc finger protein be either Cys or His residues. Furthermore, the claims require that at least one of the two amino terminal zinc coordinating residues is a His residue and at least one of the two carboxy terminal zinc coordinating residues be a Cys residue. In other words, the claimed proteins include at least one zinc finger of the CHCC, CHHC, CHCH, HCCC,

HCHC, CHCH, HHCH, HHHC, or HCCH type. As acknowledged, Barbas fails to teach polynucleotides encoding any of these non-canonical zinc finger proteins.

Moreover, Green also fails to teach such proteins. In particular, none of the non-canonical proteins disclosed in Green include at least one amino terminal His residue and at least one carboxy terminal Cys residue. Rather, Green's alterations to two naturally occurring Cys2His2 proteins result in either CCCC fingers or fingers with HisAlaCysCys zinc coordinating residues. See, e.g., Abstract and Fig. 1 of Green. Clearly, the Cys4 finger structure does not contain at least one His residue as an amino terminal zinc coordinating residue and the HisAlaCysCys finger does not comprise either Cys or His residues as the zinc coordinating residues, as required by the pending claims. Accordingly, Green does not teach all the elements as claimed and does not make up for the deficiencies of Barbas.

The obviousness rejection is also improper because the Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. ___, 127 S. Ct. 1727 (2007). Indeed, secondary considerations such as unexpected results must be considered in determining obviousness. See, also, Patent Office "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. Vol. 72, No. 195, October 10, 2007"):

Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved need, failure of others, and unexpected results. For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

In the instant case, the cited art fails to provide any evidence that zinc finger proteins with the CysHis-containing zinc coordinating residues as claimed would bind to their target sequences. As noted above, neither Green nor Barbas teach or suggest that

the particular modifications to the zinc coordinating residues as set forth in the claims result in a functional protein.

Not only do the references fail entirely to teach or suggest the particular non-canonical zinc fingers as claimed, the evidence of record establishes that it was completely unexpected that alterations as claimed would result in functional proteins. In particular, Miura (Ref. C-9 of IDS submitted April 11, 2003 and considered February, 2005) teaches that (Miura, Abstract):

Exchange of the ligand amino acid residues, i.e., cysteines to histidines and vice versa, produces a striking effect on the folding of the peptide. The beta-sheet-->alpha-helix transition is induced only by the Zn(II)-cysteine binding and the ligand exchanged peptide is not capable of folding into the finger structure.

In addition, Thukral (Ref. C137 of IDS submitted May 9, 2005 and considered November 12, 2005) teaches that mutations to zinc finger proteins can abolish *in vivo* transactivation even when the mutants bound with high affinity to their cognate binding site. (See, Abstract of Thukral).

Notably, Green does not show that their Cys4 proteins function *in vivo*. Therefore, is entirely surprising and unexpected that altering the zinc coordinating residues to the claimed non-canonical Cys and His configurations (not taught or suggested in Green or Barbas) would result in functional proteins.

In sum, given Green's failure to teach (1) non canonical zinc fingers containing Cys and His residues and (2) that Cys4 zinc finger proteins function *in vivo*, one of skill in the art would have had no reason to arrive at the claimed invention. Accordingly, a *prima facie* case of obviousness has not been and cannot be established and the rejections should be withdrawn.

CONCLUSION

In light of the amendments and remarks presented herein, it is believed that the elected subject matter is in condition for allowance. Applicants therefore request examination of generic subject matter. If the Examiner believes that a telephone conversation would expedite prosecution, she is invited to contact the undersigned at the telephone number given below.

Respectfully submitted,

Date: March 24, 2008

By: 

Dahna S. Pasternak
Registration No. 41,411

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440